(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 March 2002 (21.03.2002)

PCT

(10) International Publication Number
WO 02/22108 A1

(51) International Patent Classification[7]: A61K 9/32, 9/34, 9/36, 9/54, 9/58, 9/60, 9/62

(21) International Application Number: PCT/US01/28331

(22) International Filing Date:
10 September 2001 (10.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/659,222 11 September 2000 (11.09.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/22108 A1

(54) Title: PHARMACEUTICAL FORMULATIONS CONTAINING A NON-STEROIDAL ANTIINFLAMMATORY DRUG AND A PROTON PUMP INHIBITOR

(57) Abstract: An oral solid dosage form includes a therapeutically effective amount of an NSAID and a proton pump inhibitor in an amount effective to inhibit or prevent gastrointestinal side effects normally associated with the NSAID. Also disclosed is a method of treating a human patient in need of antiinflammatory, analgesic and/or antipyretic therapy, comprising orally administering to the patient an oral pharmaceutical dosage form which includes a therapeutically effective amount of an NSAID and an amount of a proton pump inhibitor effective to substantially inhibit gastrointestinal side effects of the NSAID. The invention is further related to a method of prophylactically treating a human patient who is on a therapy known to have significant gastrointestinal side effects or is about to begin such a therapy, via concurrent administration of an NSAID and a proton pump inhibitor in a combination (single) oral dosage form.

Other measures which can be taken to decrease GI side affects associated with NSAID therapy is to coadminister an H_2 blocker e.g. ranitidine, or a prostaglandin analogue, e.g. misoprostol, with the NSAID. In fact, a combination tablet containing diclofenac sodium and misoprostol (Arthrotec®, Pharmacia Corp.) has had FDA approval since 1988.

There is a continuing need for analgesic medications able to provide high efficacy pain relief while reducing the possibility of undesirable effects. Non-steroidal anti-inflammatory drugs, including compounds such as ibuprofen, ketoprofen and diclofenac, have anti-inflammatory actions and are effective on pain associated with the release of prostaglandins and other mediators of inflammation. For example, diclofenac and pharmaceutically acceptable salts thereof, e.g. diclofenac sodium, are considered to be extremely potent and effective as an analgesic and anti-inflammatory agent. Diclofenac is approved in the United States for the long-term symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is also considered to be useful for the short-term treatment of acute musculoskeletal injury, acute shoulder pain, postoperative pain and dysmenorrhea. However, NSAIDs such as diclofenac produce side effects in about 20% of patients that require cessation of medication. Side effects include, for example, gastrointestinal bleeding and the abnormal elevation of liver enzymes.

Non-steroidal anti-inflammatory drugs (NSAIDs) exert most of their anti-inflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Inhibition of COX-1 causes a number of side effects including inhibition of platelet aggregation associated with disorders of coagulation, and gastrointestinal side effects with the possibility of ulcerations and of hemorrhage. It is believed that the gastrointestinal side effects are due to a decrease in the biosynthesis of prostaglandins which are cytoprotective of the gastric mucosa.

For years, neutralization of gastric acid with antacids was the only relief from the pain of ulcers. However, more recently, a class of antisecretory agents that do not exhibit anticholinergic or H_2 histamine antagonistic properties, but that suppress gastric acid secretion by the specific inhibition of the H^+, K^+ - ATPase enzyme system at the secretory surface of the gastric parietal cell, has been developed. These agents (hereinafter "proton pump inhibitors") provide a more specific class of inhibitors of gastric acid secretion in mammals and man by blocking the final step of acid production.

Generally, proton pump inhibitors, their single enantiomers or alkaline salts thereof, are used for the prevention and treatment of gastric acid related diseases including, but not limited to, reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. These proton pump inhibitors may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent acid aspiration of gastric acid and to prevent and treat stress ulceration. Also, they may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these. Additionally, these proton pump inhibitors may be used for the treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable, such as patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, in patients with gastrinomas, and in particular in patients on NSAID therapy.

U.S. Patent No. 5,817,338 (Bergstrand, et al.) describes multiple unit tableted dosage forms of omeprazole, a proton pump inhibitor commercially available for inhibiting gastric acid secretion in humans. Therein, it is suggested that omeprazole may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable, e.g., in patients on NSAID therapy. However, this patent does not describe pharmaceutical formulations combining a proton pump inhibitor such as omeprazole with an NSAID.

The invention is further directed to a solid oral dosage form comprising

a) an NSAID (e.g. diclofenac or a pharmaceutically acceptable salt thereof) extended release tablet and

b) an enterically coated proton-pump inhibitor without a separating layer between the proton pump inhibitor and the enteric coat.

The invention is further directed to a (non-steroidal) antiinflammatory, analgesic, and antipyretic oral therapy which does not possess any substantial gastrointestinal side-effects, comprising an orally administrable dosage form comprising a therapeutically effective amount of an NSAID and an amount of a proton pump inhibitor effective to substantially inhibit gastrointestinal side effects of the NSAID, together with one or more pharmaceutically acceptable excipients.

The invention is further directed to a dosage form comprising a therapeutically effective amount of an NSAID and an amount of a proton pump inhibitor effective to substantially inhibit gastrointestinal side effects of the NSAID, wherein said proton pump inhibitor is coated with a material suitable to prevent contact of said proton pump inhibitor with acidic gastric juice (e.g. an enteric coating). In preferred embodiments, the material is directly coated onto the proton pump inhibitor without a separating layer between the material and the proton pump inhibitor.

The invention is further directed to the prophylactic treatment of a human patient who is on NSAID therapy or is about to begin NSAID therapy, via the concurrent administration of a proton pump inhibitor.

The invention is further directed to the prophylactic treatment of a human patient who is on a therapy known to have significant gastrointestinal side effects or is about to begin such a therapy, via the concurrent administration of a proton pump inhibitor.

For purposes of this disclosure, all references to proton pump inhibitors and NSAIDs include their single enantiomers and their pharmaceutically acceptable salts.

For purposes of this disclosure, the phrase "substrates" is meant to encompass inert pharmaceutically acceptable beads, particles, granules or pellets.

For purposes of this disclosure, the phrase "combination pharmaceutical" shall be understood to include any drug composition containing at least two therapeutically active components of which at least one is a non-steroidal antiinflammatory drug. The term "pain-alleviating" shall be understood herein to include the expressions "pain-suppressing" and "pain-inhibiting" as the invention is applicable to the alleviation of existing pain as well as the suppression or inhibition of pain which would otherwise ensue from an imminent pain-causing event.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG.1 is a graph of in vitro dissolution data which shows the dissolution profile of omeprazole from the initial formulation of Example 1 and the formulation of Example 1 after exposure to accelerated storage conditions of 40°C and 75% relative humidity for 2 weeks. The dissolution medium is a 0.5 M Phosphate buffer at a pH 6.8.

FIG. 2 is a graph of in vitro dissolution data which shows the dissolution profile of diclofenac from the initial formulation of Example 1 and the formulation of Example 1 after exposure to accelerated storage conditions of 40°C and 75% relative humidity for 2 weeks. The dissolution medium is a 0.5 M Phosphate buffer at a pH 6.8.

FIG. 3 is a graph of in vitro dissolution data which shows the dissolution profile of diclofenac from the initial formulation of Example 2, the formulation of Example 2 after

piroxicam, tebufelone, ibuprofen, etodolac, nabumetone, tenidap, alcofenac, antipyrine, aminopyrine, dipyrone, aminopyrone, phenylbutazone, clofezone, oxyphenbutazone, prexazone, apazone, benzydamine, bucolome, cinchopen, clonixin, ditrazol, epirizole, fenoprofen, floctafeninl, flufenamic acid, glaphenine, indoprofen, ketoprofen, meclofenamic acid, mefenamic acid, niflumic acid, phenacetin, salidifamides, sulindac, suprofen and tolmetin. The salicylates may include acetylsalicylic acid, sodium acetylsalicylic acid, calcium acetylsalicylic acid, salicylic acid, and sodium salicylate.

NSAIDs have been widely used in arthritis therapy for several years. The following references, hereby incorporated by reference, describe various NSAIDs suitable for use in the invention described herein, and processes for their manufacture: U.S. Pat. No. 3,558,690 to Sallmann and Pfister, (assigned to Ciba Geigy), issued 1971; U.S. Pat. No. 3,843,681 (assigned to American Home Products), issued 1974; U.S. Pat. No. 3,766,263 to Godfrey, (assigned to Reckitt and Colman) issued 1973; U.S. Pat. No. 3,845,215 to Godfrey (assigned to Reckitt and Colman) issued 1974; U.S. Pat. No. 3,600,437 to Marshall (assigned to Eli Lilly), issued 1971; U.S. Pat. No. 3,228,831 to Nicholson and Adams, (assigned to Boots Pure Drug), issued 1966; (U.S. Pat. No. 3,385,886 to Nicholson and Adams, (assigned to Boots Pure Drug) issued 1968; U.S. Pat. No. 3,161,654 to Shen, (assigned to Merck & Co.), issued 1964; U.S. Pat. No. 3,904,682 to Fried and Harrison, (assigned to Syntex), issued 1975; U.S. Pat. No. 4,009,197 to Fried and Harrison, (assigned to Syntex), issued 1977; U.S. Pat. No. 3,591,584 to Lombardino (assigned to Pfizer) issued 1971; U.S. Pat. No. 5,068,458 to Dales et al., (assigned to Beecham Group, PLC.), issued Nov. 26, 1991; U.S. Pat. No. 5,008,283 to Blackburn et al. (assigned to Pfizer, Inc.), issued Apr. 16, 1991; and U.S. Pat. No. 5,006,547 to Loose (assigned to Pfizer), issued Apr. 9, 1991. All of the above patents are hereby incorporated by reference.

Proton pump inhibitors (PPI) are potent inhibitors of gastric acid secretion, inhibiting H^+, K^+ - ATPase, the enzyme involved in the final step of hydrogen ion production in the parietal cells. The term proton pump inhibitor includes, but is not limited to, omeprazole, lansoprazole,

Lansoprazole is typically administered about 15-30 mg/day; rabeprazole is typically administered 20 mg/day and pantoprazole is typically administered 40 mg/day. However, any therapeutic or sub-therapeutic dose of these agents is considered within the scope of the present invention.

The proton pump inhibitor(s) included in the dosage forms of the invention are preferably protected from contact with acidic gastric juice, and preferably is transferred without exposure to gastric fluid until the dosage form reaches a part of the gastrointestinal tract where the pH is near neutral and where rapid absorption of omeprazole can occur.

In preferred embodiments of the invention, the pharmaceutical compositions containing the proton pump inhibitors and NSAIDs set forth herein are administered orally. Such oral dosage forms may contain one or both of the drugs in immediate or sustained release form. The oral dosage forms may be in the form of tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, multiparticulate formulations, syrups, elixirs, and the like.

The combination of proton pump inhibitor and a NSAID can be employed in admixtures with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for oral, parenteral, nasal, intravenous, subcutaneous, enteral, or any other suitable mode of administration, known to the art. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelate, carbohydrates such as lactose, amylose or starch, magnesium stearate talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, coloring, flavoring and/or aromatic substances and the like. They can

transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption of the medication can occur. Formulations which address the degradation of proton pump inhibitors in acidic media are described in U.S. Patent No. 4,786,505, 5,817,338; and 5,798,120, each of which is hereby incorporated by reference, and each of the described formulations in those patents can be modified to include one or more NSAIDs pursuant to the present invention.

One preferred embodiment of the invention is a combination pharmaceutical composition having two active ingredients, comprising a proton pump inhibitor and a NSAID in a single composition, in which the proton pump inhibitor is in the form of individually enteric coated substrates layered onto an NSAID tablet. The enteric coating layer(s) covering the substrates of the proton pump inhibitor (with or without the NSAID) is preferably sufficient to provide acid resistance to the substrates. Preferably, the enteric coating layer covering the substrates disintegrates/dissolves rapidly in near neutral or alkaline media.

In formulations prepared using multiparticulate substrates comprising enterically coated proton pump inhibitor, such multiparticulates may be mixed with NSAID (e.g., in particulate or powder form) and then separated into unit doses. Alternatively, the enterically coated substrates containing the proton pump inhibitor may thereafter by coated with the NSAID (with or without further optional overcoatings are described in more detail below). Alternatively, two separate populations of substrates may be used, one population of substrates being coated with the proton pump inhibitor and thereafter enteric-coated, the other population of substrates comprising the NSAID. The NSAID-containing substrates may comprise inert beads coated with the NSAID, or may comprise a plurality of immediate release matrices containing the NSAID. Thereafter, requisite amounts of each of the two populations of substrates could be incorporated into tablets, or into gelatin capsules, for example.

magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2 12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned substrate can be prepared by using spray drying or spray congealing technique.

The proton pump inhibitor omeprazole has an asymmetric centre in the sulfur atom, i.e. exists as two optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two enantiomers are suitable for the pharmaceutical formulation according to the present invention. A suitable form of omeprazole for preparation of multiparticulate dosage forms in accordance with the invention can be the magnesium salt of omeprazole with a specific degree of crystallinity and other physical properties disclosed in WO 95/01977, hereby incorporated by reference. Other suitable forms of the active substance are the sodium, potassium, magnesium and calcium salts of the single enantiomers of omeprazole, especially in their crystalline form described in WO 94/27988, hereby incorporated by reference.

Before applying enteric coating layer(s) onto the substrate, the substrates may optionally be covered with one or more separating (intermediate) layers, however, in preferred embodiments, the enteric coating is applied directly onto the proton pump inhibitor without the need for a separating layer.

Preferably, one or more enteric coating layers are applied onto the substrate using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents. As enteric coating layer polymers one or more,

The enteric coated substrates may then be mixed with tablet excipients (and with the NSAID in certain embodiments) and compressed into a multiple unit tableted dosage form according to the present invention, or alternatively incorporated as unit doses in appropriately sized gelatin capsules. Compressed tablets prepared in accordance with the invention are optionally covered with a film-forming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a tablet coating layer may further comprise additives like anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance. The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coated substrates. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness, of the enteric coating layer(s) must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished and that the acid resistance does not decrease more than 10% during the compression of pellets into tablets.

In certain preferred embodiments, where the NSAID is incorporated into the formulation after the enteric coating of the proton pump inhibitor substrates, the addition of the NSAID after the addition of the enteric coating to the substrates allows for rapid release of the NSAID and delayed release of proton pump inhibitor. The NSAID may be present in an outer coating in a form that does not retard its release, or may be separately incorporated into the formulation as set forth above.

Optionally soft gelatin capsules can be manufactured by filling a composition comprising the active ingredients as mentioned above and a known vegetable oil into capsules. Hard gelatin capsules can also be manufactured by filling into capsules the tablet, granules or pellets, each comprising an active ingredient as mentioned above, and a solid particulate carrier such as

may optionally include a sustained released carrier which is incorporated into a matrix along with the drug(s), or the sustained release carrier can be applied as a sustained release coating. The sustained release dosage form may comprise a plurality of substrates which include the NSAID and/or the NSAID and the proton pump inhibitor. The substrates may comprise matrix spheroids or may comprise inert pharmaceutically acceptable beads which are coated with the drug(s). The coated beads may then be overcoated with a sustained release coating comprising the sustained release carrier. The matrix spheroid may include the sustained release carrier in the matrix itself; or the matrix may comprise a normal release matrix containing the drugs, the matrix having a coating applied thereon which comprises the sustained release carrier. In yet other embodiments, the oral solid dosage form comprises a tablet core containing the drugs within a normal release matrix, with the tablet core being coated with a sustained release coating comprising the sustained release carrier. In yet further embodiments, the tablet contains the drugs within a sustained release matrix comprising the sustained release carrier. In yet further embodiments, the tablet contains the NSAID within a sustained release matrix and the proton pump inhibitor coated into the tablet in an enteric coated layer. In yet further embodiments, the dosage form comprises a plurality of multiparticulates comprising the NSAID in sustained release form (e.g., prepared in any of the manners set forth above) together with a population of a plurality of multiparticulates comprising the proton pump inhibitor in an acid-protected form (e.g., enteric coated).

The dosage forms of the present invention may optionally be coated with one or more materials suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal fluid. A pH-dependent coating serves to release the proton pump inhibitor in desired areas of the gastro-intestinal (GI) tract, e.g., the small intestine, such that an absorption profile is provided which is capable of providing at least about twelve hour and preferably up to twenty-four hour relief to a patient. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible and preferable to formulate

is diclofenac or a pharmaceutically acceptable salt thereof and the proton pump inhibitor is omeprazole or a pharmaceutically acceptable salt thereof.

The retardant material which may be included in the matrix with the NSAID can include one or more pharmaceutically acceptable hydrophobic materials and/or hydrophilic materials which are capable of imparting controlled release of the active agent in accordance with the present invention.

The hydrophobic material is preferably selected from the group consisting of waxes, alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, hydrogenated castor oil, hydrogenated vegetable oil, gums, protein derived materials, aliphatic alcohols or mixtures thereof.

In certain embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In other embodiments, the hydrophobic material is selected from materials such as alkylcelluloses, e.g. methylcellulose or ethylcellulose. In other embodiments, the hydrophobic material is an aliphatic alcohol, e.g. lauryl alcohol, myristyl alcohol, or stearyl alcohol.

An example of a suitable retardant material having hydrophilic properties is a hydroxyalkylcellulose, e.g. hydroxypropylmethylcellulose.

organic solvents are, e.g., isopropyl alcohol, ethanol, and the like, with or without water. Aqueous solvents are preferred for the overcoating procedures.

The proton pump inhibitor is coated onto the tablet. Preferably, a solution of the proton pump inhibitor is spray dried onto the surface of the tablet using any spray technique known to those skilled in the art. This coating can also be applied using a coating pan or a fluidized bed using an organic, aqueous or a mixture of an organic and aqueous solvent for the proton pump inhibitor. Preferably, aqueous solvents are preferred for the proton pump inhibitor coating.

The material suitable to prevent contact of said proton pump inhibitor with acidic gastric juice after oral administration is then overcoated onto the proton pump inhibitor coated matrix. This material preferably contains an enteric polymer. Examples of suitable enteric polymers include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures of any of the foregoing. A suitable commercially available enteric material, for example is sold under the trademark Eudragit™ L 100–555. as defined above. This coating can be spray coated onto the substrate as previously mentioned with respect to the other layers of this embodiment of the invention. Preferably, the coating to prevent contact of said proton pump inhibitor with acidic gastric juice is applied directly over the proton pump inhibitor without an intermediate separating layer.

In another preferred embodiment of the invention, the oral solid dosage form comprises a compressed matrix comprising (i) an NSAID or a salt thereof and a retardant material in an effective amount to provide a controlled release of the NSAID for at least about 24 hours and (ii) a plurality of particles comprising a proton pump inhibitor in a sufficient amount to provide an effective dose of the proton pump inhibitor to inhibit or prevent gastrointestinal side effects associated with diclofenac treatment. Preferably, the NSAID is diclofenac or a pharmaceutically

In embodiments where the NSAID is included in sustained release form, the amount of NSAID included will generally be based upon a multiple of the amount administered in immediate release form, depending of course upon the dosage frequency. In general, when the proton pump inhibitor is incorporated in sustained release form as well as the NSAID, the amount of proton pump inhibitor will remain within the same limits as set forth above with respect to enteric release forms.

DETAILED DESCRIPTION OF CERTAIN PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

Preparation of

Diclofenac sodium Extended-release/Omeprazole Delayed-release Tablets, 100/20 mg

The above formulation was prepared by preparing diclofenac extended release (ER) granules and compressing the granules into tablets. The tablets are were seal coated, followed by spray coating with an omeprazole suspension. The omeprazole coated tablet was then enteric coated, followed by a color coating.

In particular, the ingredients as set forth below in Table 1 were granulated to form Diclofenac Sodium ER Granules:

The Diclofenac Sodium ER/Omeprazole IR tablets, 100/20 mg were then enteric coated with the ingredients set forth in Table 3. The enteric coating was applied directly onto the immediate release omeprazole layer without an intermediate separating layer.

TABLE 3

Ingredients	%Weight
Diclofenac Sodium ER/Omeprazole DR Tablets	90.462
Hydroxypropyl Methylcellulose Phthalate 50, NF	4.637
Talc, USP	4.637
Cetyl Alcohol, NF	0.265
Isopropyl Alcohol, USP*	*
Acetone, NF*	*
Total	100.000

*Evaporated during the coating process

These enteric coated tablets were then color coated with an aqueous solution of Opadry White to form the final product.

The dissolution profile of omeprazole from the Diclofenac Sodium ER/Omeprazole DR tablets in a 0.5 M Phosphate buffer medium at a pH 6.8 is set forth in Figure 1 and Table 4 below:

TABLE 4

Amount Dissolved (% Omeprazole)

Time (min)	V1	V2	V3	V4	V5	V6	Mean	%RSD	Min.	Max
0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	1	0	245	0	1
10	13	16	13	22	25	20	18	27	13	25
20	86	89	81	82	81	88	85	4	81	89
30	92	93	92	90	86	95	91	3	86	95

EXAMPLE 2

Preparation of

Diclofenac sodium ER/Omeprazole DR Capsules, 100/20 mg

The above formulation was prepared by preparing diclofenac extended release granules and compressing the granules into tablets, followed by a seal coating. Delayed release enteric coated omeprazole pellets were then prepared and encapsulated with the extended release diclofenac tablet.

In particular, Diclofenac Sodium ER Tablets, 100 mg (Seal Coated) tablets were prepared in accordance with Example 1.

Omeprazole Active Pellets were prepared by coating inert beads with an omeprazole suspension in accordance with the ingredients set forth in Table 6 below:

TABLE 6

Ingredients	%Weight
Sugar Sphere, NF (18/20)	69.700
Omeprazole, USP (micronized)	14.000
Polysorbate 80, NF	1.250
L-Arginine Base, USP	0.250
D-Mannitol, USP	14.000
Povidone, USP (Plasdone K-90)	0.800
Purified Water, USP*	*
Total	100.000

*Evaporated during the coating process

The omeprazole active pellets were then enteric coated with the ingredients set forth in Table 7. The enteric coating was applied directly onto the omeprazole pellets without an intermediate separating layer.

The dissolution profile of omeprazole from the Diclofenac Sodium ER/Omeprazole DR capsules in a 0.5 M Phosphate buffer medium at a pH 6.8 is set forth in Figure 4 and Table 9 below:

TABLE 9

Amount Dissolved (% Omeprazole)

Time (min)	V1	V2	V3	V4	V5	V6	Mean	%RSD	Min.	Max
0	0	0	0	0	0	0	0	0	0	0
5	3	3	5	6	4	10	5	50	3	10
10	59	58	66	71	55	71	64	11	55	71
20	86	86	87	89	82	88	86	3	82	89
30	87	87	86	89	82	88	87	3	82	89

Capsules were then exposed to accelerated storage conditions of 40°C and 75% relative humidity for 2 weeks. The dissolution of diclofenac from the accelerated storage capsules in a 0.5 M Phosphate buffer medium at a pH 6.8 showed the formulation to be stable.

EXAMPLES 3-7

In Example 3, Diclofenac Sodium ER Tablets are prepared and seal coated in accordance with Example 1. These seal coated tablets are then sprayed with an aqueous lansoprazole solution or suspension and enteric coated in accordance with the drug layering and enteric coating procedures of Example 1. The final dosage form contains 100 mg diclofenac sodium and 15 mg lansoprazole.

In Example 4, Diclofenac Sodium ER Tablets are prepared and seal coated in accordance with Example 1. These seal coated tablets are then sprayed with an aqueous pantoprazole solution or suspension and enteric coated in accordance with the drug layering and enteric

coated pellets to provide 40 mg pantoprazole are then encapsulated with the Diclofenac Sodium ER seal coated tablet to form Diclofenac Sodium ER/Pantoprazole DR Capsules, 100/40 mg.

In Example 10, Diclofenac Sodium ER Tablets are prepared and seal coated in accordance with Example 2. Rabeprazole Active Pellets are prepared and enteric coated in accordance with the bead layering and enteric coating procedures of Example 2. A sufficient amount of enteric coated pellets to provide 20 mg rabeprazole are then encapsulated with the Diclofenac Sodium ER seal coated tablet to form Diclofenac Sodium ER/Rabeprazole DR Capsules, 100/20 mg.

In Example 11, Diclofenac Sodium ER Tablets are prepared and seal coated in accordance with Example 2. Esomeprazole Active Pellets are prepared and enteric coated in accordance with the bead layering and enteric coating procedures of Example 2. A sufficient amount of enteric coated pellets to provide 20 mg esomeprazole are then encapsulated with the Diclofenac Sodium ER seal coated tablet to form Diclofenac Sodium ER/Esomeprazole DR Capsules, 100/20 mg.

In Example 12, Diclofenac Sodium ER Tablets are prepared and seal coated in accordance with Example 2. (+) Omeprazole Active Pellets are prepared and enteric coated in accordance with the bead layering and enteric coating procedures of Example 2. A sufficient amount of enteric coated pellets to provide 20 mg (+) omeprazole are then encapsulated with the Diclofenac Sodium ER seal coated tablet to form Diclofenac Sodium ER/(+) omeprazole DR Capsules, 100/20 mg.

In Examples 1 and 2, the specified proton pump inhibitor is in the arginine salt form. Equivalent amounts of other forms of the proton pump inhibitor such as the free base, pharmaceutically acceptable salts thereof (e.g., the sodium, potassium, magnesium, calcium and amino acid salts, or mixtures thereof) or mixtures thereof, can be utilized as well.

8. The solid dosage form of claim 6 wherein said proton pump inhibitor is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, pantoprazole, leminoprazole, single enantiomers thereof, alkaline salts thereof and mixtures thereof.

9. The solid dosage form of claim 8 wherein said proton pump inhibitor is omeprazole or a pharmaceutically acceptable salt thereof.

10. An solid dosage form for oral administration comprising

a compressed matrix tablet comprising diclofenac or a pharmaceutically acceptable salt thereof and a retardant material in an effective amount to provide a controlled release of diclofenac in an amount sufficient to provide a therapeutic effect for at least about 24 hours; and

a proton pump inhibitor coated on the surface of said matrix in an amount effective to inhibit gastrointestinal side effects associated with oral administration of said diclofenac;

said coated matrix overcoated with a material suitable to prevent contact of said proton pump inhibitor with acidic gastric juice after oral administration.

11. The solid dosage form of claim 10 wherein said proton pump inhibitor is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, pantoprazole, leminoprazole, single enantiomers thereof, alkaline salts thereof and mixtures thereof.

12. The solid dosage form of claim 11 wherein said proton pump inhibitor is omeprazole or an alkaline salt thereof.

13. The solid dosage form of claim 12 wherein said omeprazole or alkaline salt thereof is spray coated onto said matrix.

14. The solid dosage form of claim 10 wherein said material suitable to prevent contact of said proton pump inhibitor with acidic gastric juice is an enteric coating.

22. The solid dosage form of claim 21 wherein said proton pump inhibitor is omeprazole or a pharmaceutically acceptable salt thereof.

23. The dosage form of claim 20 wherein said material suitable to prevent contact of said omeprazole or pharmaceutically acceptable salt thereof with acidic gastric juice is an enteric material.

24. The solid dosage form of claim 20 wherein said retardant material is an aliphatic alcohol.

25. The solid dosage form of claim 24 wherein said aliphatic alcohol is selected from the group consisting of stearyl alcohol, cetyl alcohol and mixtures thereof.

26. The solid dosage form of claim 20 wherein said diclofenac and said retardant material are in granular form prior to compression.

27. A method of treating patients with diclofenac comprising administering the solid dosage form of claim 1.

28. A method of treating patients with diclofenac comprising administering the solid dosage form of claim 10.

29. A method of treating patients with diclofenac comprising administering the solid dosage form of claim 20.

30. A solid dosage form for oral administration comprising

a compressed matrix tablet comprising an NSAID or a pharmaceutically acceptable salt thereof and a retardant material in an effective amount to provide a controlled release of said NSAID in an amount sufficient to provide a therapeutic effect for at least about 24 hours; and

33. The dosage form of claim 30, wherein the proton pump inhibitor is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, pantoprazole, leminoprazole, single enantiomers thereof, alkaline salts thereof, and mixtures thereof.

34. The dosage form of claim 31, wherein the NSAID is selected from the group consisting of salicylates, indomethacin, flurbiprofen, diclofenac, ketorolac, naproxen, piroxicam, tebufelone, ibuprofen, etodolac, nabumetone, tenidap, alcofenac, antipyrine, aminopyrine, dipyrone, aminopyrone, phenylbutazone, clofezone, oxyphenbutazone, prexazone, apazone, benzydamine, bucolome, cinchopen, clonixin, ditrazol, epirizole, fenoprofen, floctafeninl, flufenamic acid, glaphenine, indoprofen, ketoprofen, meclofenamic acid, mefenamic acid, niflumic acid, phenacetin, salidifamides, sulindac, suprofen, tolmetin, pharmaceutically acceptable salts thereof, and mixtures thereof.

35. The dosage form of claim 31, wherein the proton pump inhibitor is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, pantoprazole, leminoprazole, single enantiomers thereof, alkaline salts thereof, and mixtures thereof.

FIGURE 2

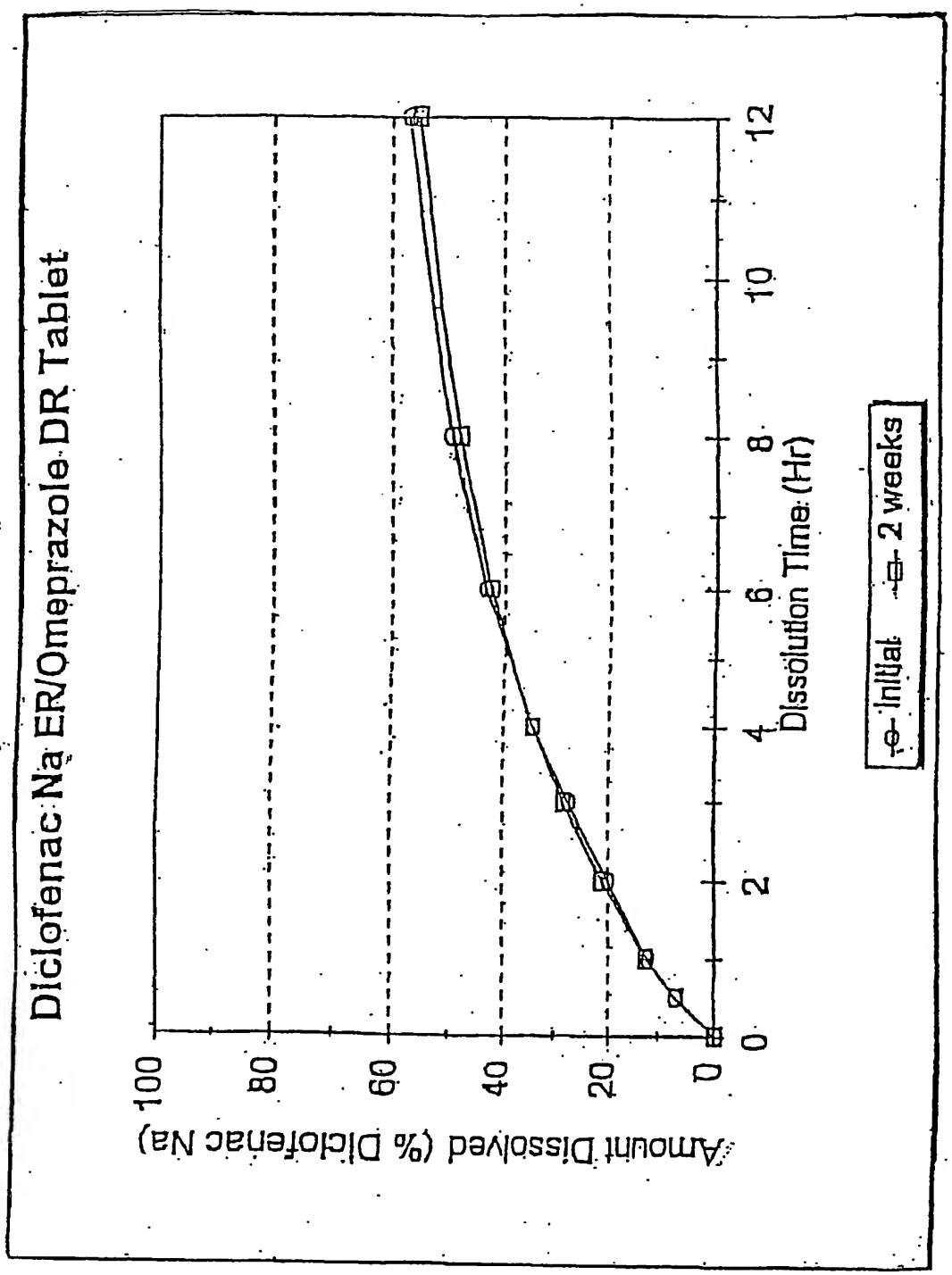
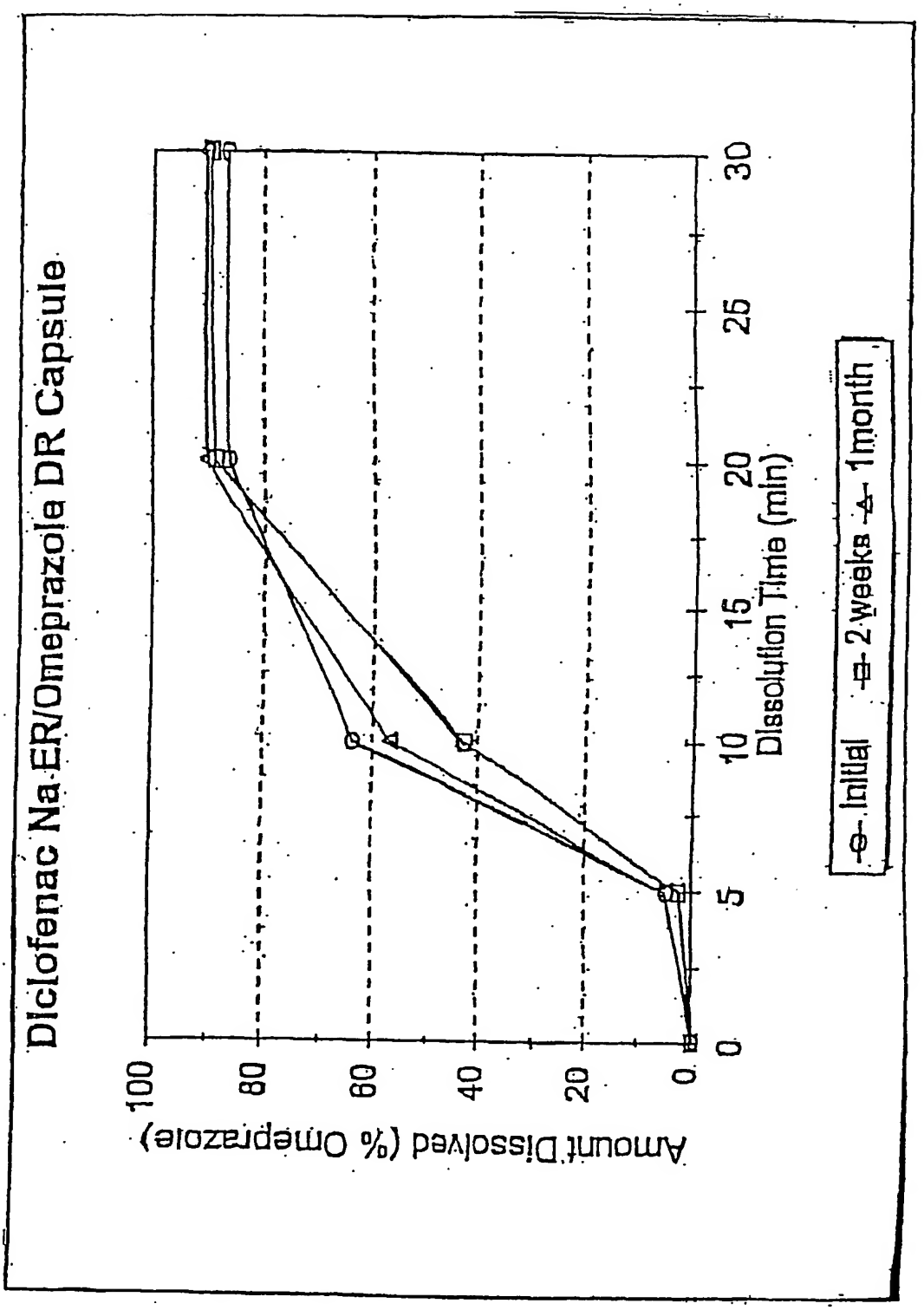

Diclofenac Na ER/Omeprazole DR Tablet
Amount Dissolved (% Diclofenac Na)
100
80
60
40
20
0
0
2
4
6
8
10
12
Dissolution Time (Hr)
Initial
2 weeks

FIGURE 4


Diclofenac Na ER/Omeprazole DR Capsule
Amount Dissolved (% Omeprazole)
100
80
60
40
20
0
0
5
10
15
20
25
30
Dissolution Time (min)
Initial
2 weeks
1month

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/28331

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/451, 455, 456, 464, 468, 469, 470, 477, 480, 481, 482, 489, 493, 494, 495, 496, 497,

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

WEST 2.0 search terms: proton, proton pump inhibitor, NSAID, antiinflammatory, diclofenac, naproxen, ibuprofen, flurbiprofen, piroxicam, omeprazole, lemiprazole, lansoprazole, rabeprazole, indomethacin, ketorolac, etodolac, salicylate,